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GEI-067

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application: Lanquetin et al.
Serial No 09/284,147
Filed on: April 7, 1999

Art Unit: 1616
Examiner: Qazi

for: New contraceptive medicinal product and method for its preparation

DECLARATION UNDER 37 C.F.R. § 1.132

Honorable Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

The undersigned, Jean-Louis THOMAS, of France, declares as follows:

I am a Medical Doctor (MD) and a Pharmacist holding such degree from the University of Nancy (France).

I have fulfilled the following functions:

1969-1972: Pharmacist Resident, Nancy hospitals

1973-1975: Consulting Pharmacist, Nancy hospitals

1975-1976: Medical Resident, Hôpital des Armées, Nancy

1976-1980: Medical Resident, Nancy hospitals

1980-1984: Assistant Resident, Centre Hospitalier Universitaire (CHU),Nancy

1984-1985: Senior Consultant-Assistant professor, CHU Nancy

1985-1987: Senior Consultant, Nancy hospitals

Since 1985: Director of the clinical Research and Development Department, Théramex Laboratory, Paris

Since 1988: Senior Consultant, Paris hospitals (Department of Endocrinology, Diabetology and Nutrition, CHU Henri-Mondor, Créteil)

I devoted many years of my professional life in the field of Endocrinology and Clinical Pharmacology.

I am the applicant of several publications, many of them on the use of hormones in women.

I direct a team that develops hormones for use in contraception and menopause.

I am a co-inventor of the captioned application.

I have read the prior art documents cited against the present application and I am of the opinion that they do not suggest the claimed method of treating estrogenic deficiencies in women.

I present hereafter the arguments which sustain my opinion.

1) Fraser (Maturitas 1989) does not suggest to use nomegestrol acetate in HRT

Fraser describes :

- **A clinical trial which had a short duration** : the aim of the study was to evaluate the effect of several doses of nomegestrol acetate on endometrium with histological and biochemical methods ; for this reason, women were treated for only 4 lunar calendars. A secretory transformation of endometrium followed by a withdrawal bleeding was observed in all cases **(Table 1)** but the endometrial effects of a long-term continuous estradiol (E2) / nomegestrol acetate treatment are not known.

- **A clinical trial using an unusual sequential HRT (Fig. 1):** nomegestrol acetate was given in a sequential manner (12 days a cycle), i.e. with interruption, and estrogenic stimulation, obtained with E2 subcutaneous implants, was continuous without treatment-free period and induced very high E2 plasma levels (see below). Consequently, it was an unusual design for a sequential HRT combination ; it was only a pharmacological model to check the short term effect of different doses of nomegestrol acetate on endometrium. Even if a regular withdrawal bleeding was observed, it is not possible to conclude, from this trial, that NOMAC could be used in HRT.

- **A clinical trial where women of the same group, receiving the same dose of nomegestrol acetate, had very different E2 plasma levels (Table 2):**

  Estradiol plasma levels did not fit with those usually obtained in HRT.

  No conclusion can be drawn as to the long-term effect of nomegestrol acetate on the endometrium.

- **A clinical trial which did not take into account vasomotor symptoms** which are the major indication for HRT.

- **A clinical trial with a high number of drop-out**
  There were 6 drop-out from 36 patients, ie 17%, during a clinical which only lasted for 4 menstrual cycles. This unusual high drop-out rate came from numerous adverse effects like bleeding and, very often, nausea, headackes, irritability and mood swings. The frequency of these adverse effects shows that the E2/ nomegestrol acetate combination given by Fraser was not suitable for HRT.

In conclusion, Fraser

shows that nomegestrol acetate induces a secretory endometrial transformation in all women

but because
- the clinical trial duration was short,
- the effects on climacteric symptoms were not evaluated
- estrogenic stimulation was continuous, very strong and different from one woman to another
- there were numerous adverse effects and numerous drop-out, making the studied treatment not suitable for long-term therapy of postmenopausal women

the skilled man would not have considered using a combination of nomegestrol acetate and an estrogen for the treatment of estrogenic deficiencies in women, a fortiori a combination to be continuously administered.

2) Plunkett (USRe 36,247) fails to disclose Nomegestrol acetate as progestin and the properties thereof

Plunkett is relied upon for teaching a continuous method of administering a progestin and an estrogen. Plunkett does not disclose nomegestrol acetate, as acknowlegded by the Examiner.

As pointed out during the interview held on June 25, 2002, nomegestrol acetate exhibits specific properties:

Nom gestrol acetat has an original pharmacological profile which is not shar d by any synth tic progestin (Table 3)

It is a potent progestin when given by the oral route
It is devoid of any residual androgenic activity
It is devoid of any residual estrogenic activity
It is devoid of any residual gluco-corticoid activity
It is devoid of any residual mineralo-corticoid activity
It has a strong antiestrogenic effect
It has a strong antiandrogenic effect
It has a strong antigonadotropic effect

❷Progestins continuously given with an estrogen induce an endometrial atrophy.

After the issue of the Plunkett's patent, nomegestrol acetate was shown to have a different effect on endometrium **(Fig 2)**; this effect is characterized by a dissociation between anti-estrogenic and progestagen activity : at low doses, the anti-estrogenic effect is predominant and endometrium is atrophic ; at high doses, the progestagen effect is predominant and the endometrium is secretory. Unexpectedly, even with high nomegestrol acetate doses, a large majority of women are amenohrreic **(Fig 2).** This is a characteristic of nomegestrol acetate, never described for other progestins, which can bring clinical advantages, especially in term of acceptability of treatment and consequently compliance, due to an increase of the percentage of no-bleeding pattern.

The skilled man would not have been motivated to use a progestin and an estrogen continuously as taught by Plunkett and to use nomegestrol acetate as progestin because Fraser does not provide any incentive to do so. In addition, the effects of nomegestrol acetate on the endometrium are surprising and unexpected when taken in the light of the cited prior art.

3) Lanquetin (US 5,891,867) does not teach the method claimed in the present application

For reasons already of record, Lanquetin does not teach a method of continuously (i.e. without interruption) administering a progestin and an estrogen. Indeed, Lanquetin teaches a trisequential treatment, with first estradiol alone, then with the estradiol/nomegestrol acetate combination and then with a placebo. This trisequential method results in menstrual bleeding and reproduces in post menopausal women the woman's normal cycle.

In contrast, the method claimed in the present application relates to the administration of both estradiol and nomegestrol acetate given simultaneously with no interruption and avoids menstrual bleeding (no bleeding pattern).

Table 1 : Clinical and nd m trial diff r nc s b tw n Fras r publicati n and Lanqu tin US Pat nt n° 5,891,867 vis-àvis curr nt application n° 284,147

	FRASER publication	Lanquetin's patent US Patent 5,891,867	Application N° 284,147 (GEI-067)
Treatment regimen	Sequential treatment	Sequential treatment	Continuous treatment
Menstrual Cycle	Regular	Regular	Absent
Bleeding	Withdrawal bleeding	Withdrawal bleeding	No bleeding
Endometrium	Secretory	Secretory	Atrophic/Secretory depending on dose

Table 2 : Fraser's publication: mean E2 plasma levels (pmol/l) in women of each group

NOMAC dose	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12
0.5	830	**1837**	451	1350	793	711	1235	1012	708	581	**284**	919
1	998	590	922	791	1600	364	630	1250	**1525**	**202**	556	673
2.5	830	**1837**	451	1350	793	711	1235	1012	708	581	**284**	919

Table3 : comparison of pharmacological profile of nomegestrol acetate and other progestins

NOMAC	OTHER PROGESTINS	
	Progesterone derivatives	19-nor testosterone derivatives
Strong progestagen activity	Strong progestagen activity except progesterone	
without androgenic residual effects without estrogenic residual effects without gluco-corticoid residual effects without deleterious metabolic effects	with or without androgenic residual effects without estrogenic residual effects with or without gluco-corticoid residual effects with or without deleterious metabolic effects	with androgenic residual effects with estrogenic residual effects with gluco-corticoid residual effects with deleterious metabolic effects
Strong antigonadotropic activity	Only slight antigonadotropic activity	Strong antigonadotropic activity

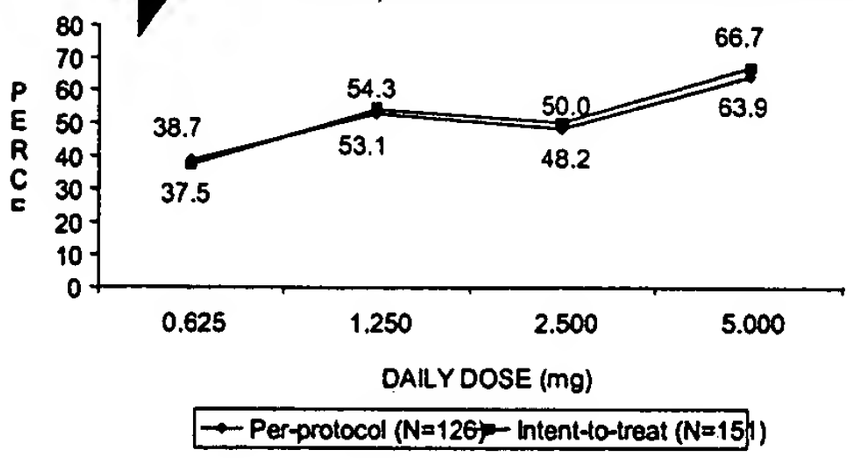
Figure 1
DIFFERENCES between Lanquetin's US patent 5,891,867, Fraser's Publication and Current application n° 284,147

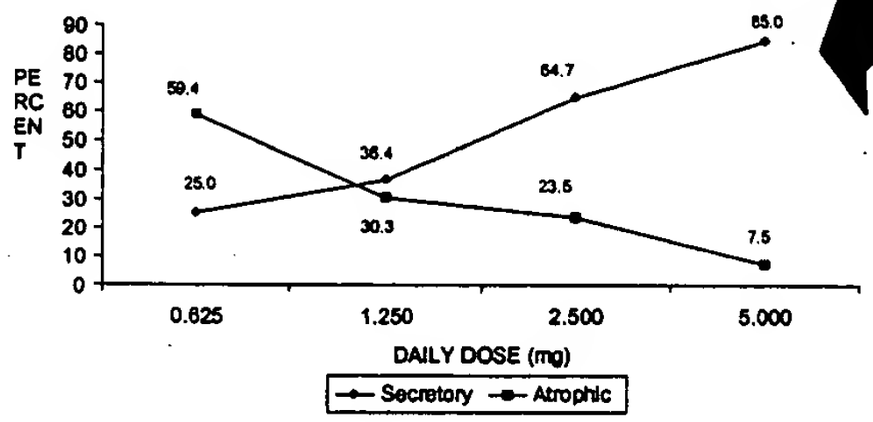
Figure 2 : End metrial ff cts of E2/n meg strol acetat continu us combination

Clinical examples

151 postmenopausal wom(treated for 6 months)

Dose E2V mg - NOMAC mg	2.0 0.625	2.0 1.25	2.0 2.5	2.0 5.0
Number of patients	37	37	38	38
Amenorrhea (%)	38.7	54.3	50.0	66.7
Secretory endometrium (%)	25.0	36.4	64.7	85.0
Atrophic endometrium (%)	59.4	30.3	23.5	7.5





I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed this 25th day of June 2003

Jean-Louis THOMAS